

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing

(day/month/year)

03 December 2024 (03.12.2024)

Applicant's or agent's file reference

BCR-006WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2024/019416

International filing date (day/month/year)

11 March 2024 (11.03.2024)

Priority date (day/month/year)

09 March 2023 (09.03.2023)

International Patent Classification (IPC) or both national classification and IPC

IPC: **C12N 15/113** (2024.01); **A61K 31/713** (2024.01); **A61P 9/00** (2024.01)

CPC: **C12N 15/1136; A61K 31/713; A61P 9/00; C12N 2310/11; C12N 2310/31; C12N 2310/321; C12N 2310/322**

Applicant

BASECURE THERAPEUTICS LLC

1. This opinion contains indications relating to the following items:



Box No. I

Basis of the opinion



Box No. II

Priority



Box No. III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability



Box No. IV

Lack of unity of invention



Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement



Box No. VI

Certain documents cited



Box No. VII

Certain defects in the international application



Box No. VIII

Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US

**COMMISSIONER FOR PATENTS
MAIL STOP PCT, ATTN: ISA/US
P.O. Box 1450
Alexandria, VA 22313-1450
UNITED STATES OF AMERICA**

Date of completion of this opinion

28 August 2024 (28.08.2024)

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. I

Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(b)).
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. See claims listed below

because:

- ☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 13-81 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 13-81 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 2, 13-81

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).
 - ☐ See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
- ☐ paid additional fees under protest and, where applicable, the protest fee.
- ☐ paid additional fees under protest but the applicable protest fee was not paid.
- ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-12 are drawn to double-stranded ribonucleic acids (dsRNAs) for inhibiting expression of Angiotensinogen (INHBE).

The first invention of Group I+ is restricted to an antisense strand selected to be SEQ ID NO: 598 and a sense strand selected to be SEQ ID NO: 589, and double-stranded ribonucleic acids (dsRNAs) for inhibiting expression of Angiotensinogen (INHBE) comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed element for each of the variables presented in the claims (see claim 1). It is believed that claims 1 and 3-12 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs: 589 and 598.

Applicant is invited to elect additional antisense and sense strands, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an antisense strand selected to be SEQ ID NO: 599 and a sense strand selected to be SEQ ID NO: 590, and double-stranded ribonucleic acids (dsRNAs) for inhibiting expression of Angiotensinogen (INHBE) comprising the same. Additional antisense and sense strands, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/ examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element, requiring the selection of alternative antisense and sense strands where "the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length, wherein: (a) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 598, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 589; (b) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 599, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 590; (c) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 600, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 591; (d) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 601, and the sense strand comprises a

Box No. IV Lack of unity of invention

sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 592; (e) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 602, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 593; (f) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 603, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 594; (g) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 604, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 595; (h) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 605, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 596; or (i) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 606, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 597” and where “the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length, wherein: (a) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 616, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 607; (b) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 617, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 608; (c) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 618, and the sense strand a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 609; (d) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 619, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 610; (e) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 620, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 611; (f) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 621, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 612; (g) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 622, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 613; (h) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 623, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 614; or (i) the antisense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 624, and the sense strand comprises a sequence that is at least 70% or 80% identical to the sequence of SEQ ID NO: 615.”

Additionally, even if Groups I+ were considered to share the technical features of a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Angiotensinogen (INHBE), wherein the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2023/003922 A1 to Alnylam Pharmaceuticals, Inc. (hereinafter, “Alnylam”) teaches a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Angiotensinogen (INHBE), wherein the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length (Pg. 2, Lns. 10-16, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE) ... wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1, 3-12

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Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1, 3-12	YES
	Claims	None	NO
Inventive step (IS)	Claims	1, 3-12	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1, 3-12	YES
	Claims	None	NO

2. Citations and explanations:

----- EXPLANATION -----

Claims 1 and 3-12 have been analyzed subject to the restriction that the claims read on an antisense strand selected to be SEQ ID NO: 598 and a sense strand selected to be SEQ ID NO: 589, and double-stranded ribonucleic acids (dsRNAs) for inhibiting expression of Angiotensinogen (INHBE) comprising the same.

Claims 1 and 3-12 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 1, the prior art of record, individually or in combination, does not teach or fairly suggest a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Inhibin Subunit Beta E (INHBE), wherein the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length, wherein: (a) the antisense strand comprises SEQ ID NO: 598, and the sense strand comprises SEQ ID NO: 589.

The following prior art is made of record to support and further define the reasons claim 1 meets the criteria set out in PCT Article 33(2)-(3):

(i) WO 2023/003922 A1 to Alnylam Pharmaceuticals, Inc. (hereinafter, "Alnylam") teaches a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Inhibin Subunit Beta E (INHBE), wherein the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length (the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of a metabolic disorder-associated target gene selected from the group consisting of inhibin subunit beta E (INHBE) ... wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, e.g., 15, 16, 17, 18, 19, 20, or 21, contiguous nucleotides, Pg. 2, Lns. 10-16), a nucleic acid sequence comprising 100% sequence identity to SEQ ID NO: 598 (the antisense strand comprises at least 15... contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the corresponding portion of the nucleotide sequence of any one of SEQ ID NOs: ... 8, Pg. 2, Lns. 18-21; SEQ ID NO: 8 of Alnylam comprises 100% sequence identity to instant SEQ ID NO: 598), and a nucleic acid sequence comprising 100% sequence identity to SEQ ID NO: 589 (The entire contents of all references, patents and published patent applications cited throughout this application, as well as the informal Sequence Listing and Figures, are hereby incorporated herein by reference, Pg. 138, Lns. 18-20; The Sequence Listing discloses SEQ ID NO: 5678; SEQ ID NO: 5678 of Alnylam comprises 100% sequence identity to instant SEQ ID NO: 589).

None of the prior art taken alone or in combination fairly teach or suggest a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Inhibin Subunit Beta E (INHBE) comprising the combination of SEQ ID NO: 598 and SEQ ID NO: 589, as recited above.

Claims 3-12 depend from claim 1, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 1.

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Box No. V

**Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

Claims 1 and 3-12 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 1 is indefinite for the following reason(s):

With regards to claim 1, the claim recites the phrase "Angiotensinogen (INHBE)..." which appears to be a typographical error because INHBE is the gene symbol for Inhibin Subunit Beta E. For the purposes of this written opinion, claim 1 is best interpreted to read as:

1. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Inhibin Subunit Beta E (INHBE), wherein the dsRNA comprises a sense strand and an antisense strand each 15 to 30 nucleotides in length, wherein: (a) the antisense strand comprises SEQ ID NO: 598, and the sense strand comprises SEQ ID NO: 589.